Remarks

Status of the Claims

Prior to entry of this amendment, claims 1-28, 33-36, 42, 44, 45, 47-74, 76-79, and 86-94 were pending in this application. Claims 1, 3, 5, 6, 7, 36, and 47 are amended herein, and claims 4, 18, 48-74, 76-79, 86-89, and 92-94 are cancelled. Applicants expressly reserve the right to pursue any cancelled subject matter in subsequent applications.

Support for the amendments of claim 1 can be found throughout the specification, the claims as originally filed, and at least on page 11, lines 14-15 and page 45, line 26 through page 46, line 5, claim 4, and claim 18. Claims 3, 5, 7, 36, and 47 are amended to correct dependency and/or obvious clerical errors. No new matter is introduced by this amendment.

After entry of this amendment, **claims 1-3, 5-17, 19-28, 33-36, 42, 44, 45, 47, 90, and 91 are pending**. Reconsideration of the pending claims is respectfully requested.

Amendment to the Specification

The specification is amended herein at the request of the Office to remove an embedded hyperlink. No new matter is introduced by this amendment. Applicants request that the objection to the specification be withdrawn.

Election/Restrictions

Applicants thank Examiner Shin for rejoining the claims directed to SEQ ID No. 1 and SEQ ID No. 3 for examination in the present case. Applicants expressly reserve the right to pursue any non-elected subject matter at a later date and/or in subsequent applications.

Oath or Declaration

The Office has objected to the Declaration submitted with the application upon entry into the U.S. National Stage under U.S.C. § 371, for alleged failure of that Declaration to comply with the requirements of M.P.E.P. § 602.01 and 602.02. Specifically, the Office contends that the Declaration does not properly identify the current application, and only refers to International

Application No. PCT/GB2004/004908. Applicants traverse and submit that the Declaration as filed is correct.

The current application entered the U.S. National Stage under U.S.C. § 371 and thus International Application No. PCT/GB2004/004908 is the current application. Therefore, the Declaration as filed correctly names the current application. Furthermore, under C.F.R § 1.497, an oath or declaration under 35 U.S.C. 371(c)(4)(a) is only required "[w]hen an applicant of an international application desires to enter the national stage under 35 U.S.C. 371 pursuant to § 1.495, and a declaration in compliance with this section has not been previously submitted in the international application under PCT Rule 4.17(iv) within the time limits provided for in PCT Rule 26ter.1…" The Declaration submitted with the current application complies with PCT Rule 4.17(iv) and was submitted in the international application within the time limits provided for in PCT Rule 26ter.1. Therefore no additional Declaration is required. Applicants respectfully request that the objection to the Declaration be withdrawn.

Objections to the Claims

Claims 5 and 7 have been amended to obviate the asserted objections. Claim 4 is cancelled herein, rendering the objection of claim 4 moot. In light of the amendments made herein, Applicants request that the objections to the claims be withdrawn.

Claim Rejections under 35 U.S.C. § 112, 1st paragraph

Claims 1-28, 33-36, 42, 44, 45, 90-91, and 94 have been rejected under 35 U.S.C. § 112, 1st paragraph for alleged failure to comply with the written description requirement. Specifically, the Office contends that that the specification does not provide adequate written description for the use of the genus of herpes simplex virus encoding an antisense to the squamous cell carcinoma related oncogene. Applicants respectfully disagree.

The Office contends that the written description requirement is not fulfilled because the species disclosed in the specification is not representative of the claimed genera. However, it does not automatically follow that exemplification of an invention by one species leads to a lack of adequate support. On the contrary, according to the M.P.E.P. § 2163(II)(A) the issue is rather

whether one of ordinary skill in the art would understand Applicants to have invented and be in possession of the invention as claimed. Furthermore, acording to M.P.E.P. § 2163(II)(A), "[t]he examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims." In addition, "[t]here is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed, *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976)", M.P.E.P. § 2163(I)(A).

Possession of a genus may be satisfied through sufficient description of a "representative number of species" by: (a) an actual reduction to practice, (b) a reduction to drawings, or (c) disclosure of relevant, identifying characteristics, for example structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus. In other words, possession of a genus can be evidenced by describing the distinguishing identifying characteristics common to the divergent species encompassed.

A "representative number of species" means that the species which are actually described are representative of the entire genus. Thus, when there is substantial variation with the genus, one must describe a sufficient variety of species to reflect the variation. What constitutes a representative number is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a representative number of species depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. Applicants submit that the specification describes an adequate number of species to support the breadth of the claims.

The current invention is based on the inventors' discovery that a herpes simplex virus encoding an antisense to the squamous cell carcinoma related oncogene (SCCRO) can induce cell death by cytolysis and by down regulation of endogenous SCCRO expression (see

specification at page 74, lines 22-27). As discussed above, possession of the invention can be shown by actual reduction to practice. Applicants have reduced the invention to practice by showing that a herpes simplex virus encoding an antisense to SCCRO exhibits an increase in cell-killing effect *in vitro* and *in vivo* (see Example 4, pages 74-77).

The insight and confirmatory results reported in the specification are reflected in the claims, which require that a herpes simplex virus genome includes a nucleic acid encoding an antisense to the squamous cell carcinoma related oncogene.

A person of ordinary skill in the art reading the specification would understand that the invention can be practiced with a variety of different antisense nucleic acids to SCCRO and with many different herpes simplex viruses. In addition, the specification describes in detail the methodology for inserting antisense nucleic acids in to a herpes simplex virus, such that the virus expresses the nucleic acid (see for example, pages 46-60 and Examples 1-3 on pages 60-74). In other words, a person of ordinary skill in the art would understand that the invention is not limited to particular species of antisense nucleic acids or a particular species of herpes virus.

Solely to advance prosecution of the subject application, claim 1 has been amended to narrow the claimed genus of antisense nucleic acids, such that the target squamous cell carcinoma related oncogene nucleotide sequence includes SEQ ID No. 1 or SEQ ID No. 3. The antisense nucleic acid sequence has been structurally defined as a nucleic acid sequence. In addition, the genus of herpes simplex virus has been narrowed to non-neurovirulent herpes simplex virus. Applicants submit that the claims as amended herein satisfy the requirements of 35 U.S.C. § 112, 1st paragraph with regards to the written description requirement.

Defining the antisense nucleic acids or herpes simplex viruses even more narrowly would increase the possibility that the claims could be designed around. Such a situation would not provide Applicants a fair reward for disclosing the invention to the public and demonstrating reduction to practice.

Notwithstanding the above, the claims have been amended to limit the antisense nucleotides and to limit the genera of herpes simplex viruses. Applicants submit the specification discloses a "representative number of species" in order for the person of ordinary skill in the art to recognize that Applicants were in possession of the invention as currently claimed. Applicants further submit that the claims comply with the written description requirement and request that this rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 112, 2nd paragraph

Claims 6 and 7 are rejected under 35 U.S.C. § 112, 2nd paragraph for alleged failure to particularly point out the subject matter Applicants consider their invention. Specifically, the Office contends that there is insufficient antecedent basis for "said degree of sequence identity" in claim 6. Claim 6 has been amended to recite "a nucleotide sequence having at least 70% sequence identity…" Applicants request that the rejection of claim 6 be withdrawn.

The Office also contends that claim 7, and specifically line two of that claims, is inconsistent with the length of SEQ ID No. 3, in that SEQ ID No. 3 is only 876 nucleotides. Applicants disagree. The language of claim 7 states the "fragment comprises at least 20 nucleotides and no more than 900 nucleotides." As 876 are "no more than 900 nucleotides", there is no inconsistency. Applicants request that the rejection of claim 7 be withdrawn.

Claim Rejections under 35 U.S.C. § 103(a)

Applicants have shown both *in vivo* and *in vitro,* that a herpes simplex virus encoding an antisense to the squamous cell carcinoma related oncogene (SCCRO) exhibits a greater tumor-cell killing effect than herpes simplex virus that does not encode antisense to the SCCRO. This potentially provides effective new cancer treatments.

Prior to Applicants' invention, there were no reports of using herpes simplex virus to deliver antisense molecules. Thus, prior to Applicants' invention, a person skilled in the art could not be sure whether herpes simplex virus is capable of delivering antisense molecules. For example, a person of ordinary skill in the art would not know whether herpes simplex virus would express antisense molecules in the right part of the cell, or whether herpes simplex virus

would be capable of expressing enough antisense molecules to have any effect on the target gene. Nor would a person of ordinary skill in the art know whether the herpes simplex virus itself may inhibit cellular antisense mechanisms.

Also prior to Applicants' invention, there were no reports of using antisense to SCCRO to treat squamous cell carcinoma, or any other cancer. Although Estilo *et al.* is concerned with SCCRO, it does not teach that squamous cell carcinoma may be treated by antisense to SCCRO. Thus, prior to Applicant's invention the skilled person could not know that antisense to SCCRO can successfully treat squamous cell carcinoma.

In arriving at the present invention, Applicants have shown that herpes simplex virus may deliver antisense nucleic acid, that antisense to SCCRO is effective against squamous cell carcinoma during viral infection, and that the antisense to SCCRO may be delivered by herpes simplex virus. Importantly, they have also provided *in vivo* data showing that such herpes simplex viruses are effective treatments for squamous cell carcinoma.

As none of the references cited in the Office action motivate one of ordinary skill in the art to insert antisense molecules to SCCRO into a herpes simplex virus, Applicants submit that the claims are not obvious and request that the rejections under 35 U.S.C. § 103(a) be withdrawn. Specific rejections under §103 are also addressed separately below.

Rejection of claims 1-28, 33, 36, 47, and 94

Claims 1-28, 33, 36, 47, and 94 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Nemunaitis (*Biodrugs*, 2003, 17:251-262) in view of Tang *et al.* (US 2003/0022329 A1) and Jacobs *et al.* (*Human Gene Therapy*, 2003 14:277-297). Claims 4, 18, and 94 have been canceled rendering the rejection of these claims moot.

The Office contends that it would have been obvious to one of ordinary skill in the art to insert SEQ ID NO: 22 from Tang *et al.* into the HSV mutant of Nemunaitis using the technology of Jacobs *et al.* (the Office action refers to "Johns *et al.*" but it is assumed that this was meant to refer to Jacobs *et al.* and the response to the rejection is treated accordingly).

Nemunaitis is a review of selective replicating viral vectors. The Office admits that Nemunaitis does not teach inserting an antisense to the squamous cell carcinoma related oncogene sequence into herpes simplex mutant virus. Nemunaitis also fails to teach or suggest that a herpes simplex virus can be used to deliver antisense nucleic acids. In addition, Nemunaitis does not teach a squamous cell carcinoma related oncogene nucleic acid sequence. The Office attempts to make up for the deficiencies present in Nemunaitis by first citing Tang *et al.* The Office contends that Tang *et al.* teaches that "the antisense molecule comprising SEQ ID NO: 22 can be used to inhibit squamous cell carcinoma" (see page 9 of the Office action). However, this clearly is not what Tang *et al.* teaches.

Tang *et al.* discloses 91 nucleic acid sequences that were obtained from cDNA libraries prepared from various human tissues (see paragraphs 0332 and 0335). These sequences were used in a database search to find homologues having a known function (see paragraph 0337). The references to SEQ ID NO: 22 in Tang *et al.* fail to teach any relationship between SEQ ID NO: 22 and any cancers. Tang *et al.* in Table 1 teaches that SEQ ID NO: 22 is found in adult kidney, adult ovary, bone marrow, endothelial cells, fetal liver spleen, and lymphocytes. Tang *et al.* in Table 2 teaches that SEQ ID NO: 22 is homologous to the nucleotide sequence AF198092, previously identified by Mas *et al.* (*Genomics,* 2000 Apr 1;65(1):70-4) as mRNA for *Mus. musculus* RP42 and mapped to an autism susceptibility locus on 6q16. Finally, Tang *et al.* in Table 3 teaches that SEQ ID NO: 22 has a maltose binding protein signature. None of these references to SEQ ID NO:22 suggest a role in squamous cell carcinoma. It is apparent from the Examples in Tang *et al.* that essentially no further analysis of SEQ ID NO: 22 was undertaken. Thus, one of ordinary skill in the art would understand that Tang *et al.* provides absolutely no teaching or suggestion that SEQ ID NO: 22 is associated with squamous cell carcinoma, or any other cancer for that matter.

The Office cites Tang *et al.* paragraph 0195 as suggesting that SEQ ID NO: 22 can be used to treat cancer. However, paragraph 0195 presents nothing more than a laundry list of cancer types, and does not establish any nexus between SEQ ID NO: 22 and cancer, much less squamous cell carcinoma. Tang *et al.* does not link any of the cancers listed in paragraph 0195

with any of SEQ ID NOs: 1-91. Based on the arguments presented in the Office action, the Office would have one believe that it would be obvious to one of ordinary skill in the art reading Tang *et al.* that antisense molecules to any and all of SEQ ID NOs: 1-91 could be used to treat cancer, "including in solid phase tumors/malignancies, locally advanced tumors, human soft tissue sarcomas, metastatic cancer, including lymphatic metastases, blood cell malignancies including multiple myeloma, acute and chronic leukemias, and lymphomas, head and neck cancers including mouth cancer, larynx cancer and thyroid cancer, lung cancers including small cell carcinoma and non-small cell cancers, breast cancers including small cell carcinoma and ductal carcinoma, gastrointestinal cancers including esophageal cancer, stomach cancer, colon cancer, colorectal cancer and polyps associated with colorectal neoplasia, pancreatic cancers, liver cancer, urologic cancers including bladder cancer and prostate cancer, malignancies of the female genital tract including ovarian carcinoma, uterine (including endometrial) cancers, and solid tumor in the ovarian follicle, kidney cancers including renal cell carcinoma, brain cancers including intrinsic brain tumors, neuroblastoma, astrocytic brain tumors, gliomas, metastatic tumor cell invasion in the central nervous system, bone cancers including osteomas, skin cancers including malignant melanoma, tumor progression of human skin keratinocytes, squamous cell carcinoma, basal cell carcinoma, hemangiopericytoma and Karposi's sarcoma." Such an assertion is clearly not supported (including not being enabled) by the teachings in Tang *et al.*

Furthermore, Tang *et al.* in paragraph 0196 states that the listed cancers may be treated by administering inhibitors *and* stimulators of the biological activity of the polypeptides, which clearly does not even teach whether any or all of SEQ ID NOs: 1-91 should be inhibited or stimulated. Clearly, stimulating a nucleic acid/peptide that should be inhibited could be counter-productive to the aim of the treatment and possibly lead to disastrous consequences. Stating that a treatment may involve inhibition or stimulation of any of 91 polypeptides clearly does not teach one of ordinary skill in the art how to treat any of the cancers mentioned in paragraph 0195.

With regard to SEQ ID NOs: 1-91, Tang *et al.* also mentions that, in addition to the treatment of cancer, the polypeptides may have nutritional uses (paragraph 0138), cytokine and cell proliferation/differentiation activity (paragraph 0139), stem cell growth factor activity

(paragraph 0144), hematopoiesis regulating activity (paragraph 0151), tissue growth activity (paragraph 0156), immune stimulating or suppressing activity (paragraph 0168), activin/inhibin activity (paragraph 0184), chemotactic/chemokinetic activity (paragraph 0187), hemostatic and thrombolytic activity (paragraph 0191), receptor/ligand activity (paragraph 0200), anti-inflammatory activity (paragraph 0214), use in the treatment of leukemias (paragraph 0215), use in treatment of nervous system disorders (paragraph 0216), and other activities mentioned in paragraph 0232. This further underlines the purely speculative nature of Tang *et al.*

Thus, there is no teaching in Tang *et al.* that an antisense molecule specifically comprising SEQ ID NO: 22 would be useful for specifically treating squamous cell carcinoma. Furthermore, there is no teaching in Tang *et al.* that herpes simplex virus may be successfully used to deliver such an antisense nucleic acid.

The Office further attempts to make up for the deficiencies present in Nemunaitis by citing to Jacobs *et al.* This reference teaches methods of gene therapy, and in particular teaches providing a non-invasive method of assessing the distribution of therapeutic gene expression (see Abstract). Jacobs *et al.* does not teach or suggest that herpes simplex virus may be used to deliver antisense nucleic acids. Nor does Jacobs *et al.* teach or suggest antisense molecules to SCCRO.

Applicants submit that a person of ordinary skill in the art reading Nemunaitis, Tang *et al.* and Jacobs *et al.* would not be motivated to provide an antisense molecule comprising SEQ ID NO: 22 with a reasonable expectation of successfully treating squamous cell carcinoma, or any other cancer.

The initial burden is on the Office to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). Furthermore,

"[i]n formulating a rejection under 35 U.S.C. 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed," (citing: Deputy Commissioner for Patent Operations' Memo of May 3, 2007).

In rejecting the claims, the Office has merely stated that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to insert the antisense polynucleotide of Tang *et al.* into the HSV mutant of Nemunaitis through the recombination technology of [Jacobs *et al.*]" The Office also has stated that one of ordinary skill in the art would have been motivated to do so, "because Tang *et al.* taught that the antisense polynucleotide comprising SEQ ID NO: 22 can be used to inhibit squamous cell carcinoma." However, as discussed above, in combining the references to reach the claimed invention, the Office has not considered that one of ordinary skill in the art could not reasonably infer that Tang *et al.* teaches an antisense therapy to squamous cell carcinoma. Thus, one of ordinary skill in art would not be motivated to modify the references as suggested by the Office, because based on the speculative nature of Tang *et al.*, there would be no expectation that the claimed invention would be successful.

As noted above, at a minimum obviousness requires a reasonable expectation of success. Given the teachings of Tang *et al.*, one of ordinary skill in the art clearly could not have reasonably predicted or expected that modifying the teaching of Nemunaitis according to the Office's suggestion would yield successful results. Accordingly, Applicants submit that the modifications to the prior art proposed by the Office cannot be characterized as "obvious". In view of the amendments and argument presented herein, no *prima facie* case of obviousness has been presented with respect to claims 1-3, 5-17, 19-28, 33, 36, and 47 and Applicants request that this rejection be withdrawn.

Rejection of claims 1-3, 9-18, 33-36, 42, 44, 45, 90, 91, and 94

Claims 1-3, 9-18, 33-36, 42, 44, 45, 90, 91, and 94 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Coukos *et al.* in view of Sidransky (US Patent No. 6,025,127) and

Glorioso *et al.* (International Patent Publication WO 98/51809). Claims 18 and 94 are cancelled rendering the rejection of these claims moot.

To establish *prima facie* obviousness "all the claim limitations must be taught or suggested by the prior art" (M.P.E.P. 2143.03). The prior art does not meet this burden with respect to claim 1 as amended herein, no *prima facie* case of obviousness has been established, and claim 1 is allowable. Claim 1 as amended herein includes the limitations formerly present in claim 4. As claim 4 was found allowable over the asserted combination of Coukos *et al.*, Sidransky, and Glorioso *et al.*, present claim 1 is allowable. All of the pending claims depend either directly or indirectly from claim 1, include the limitations present in claim 1, and are allowable for at least the same reasons claim 1 is allowable. Therefore, Applicants request that this rejection of claims 1-3, 9-17, 33-36, 42, 44, 45, 90, and 91 be withdrawn.

Rejection of claims 1-28, 33-36, 42, 44, 45, 90-91, and 94

Claims 1-28, 33-36, 42, 44, 45, 90, 91, and 94 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Toyoizumi *et al.* (*Human Gene Therapy,* 1999, 10:3013-3029) in view of Estilo *et al.* (*Critical Cancer Research*, 2003, 9:2300-2306), and Jacobs *et al.* Claims 4, 18, and 94 have been canceled rendering the rejection of these claims moot.

The Office has alleged that one of ordinary skill in the art would have been motivated to use any one of the disclosed mutants of Toyoizumi *et al.* as an expression vector to carry an antisense sequence to squamous cell carcinoma, with a reasonable expectation of success. To establish *prima facie* obviousness "all the claim limitations must be taught or suggested by the prior art" (M.P.E.P. 2143.03). The asserted combination of Toyoizumi *et al.*, Estilo *et al.*, and Jacobs *et al.* does not meet this burden with respect to claim 1, and no *prima facie* case of obviousness has been established with respect to claims 1-3, 5-17, 19-28, 33-36, 42, 44, 45, 90, and 91 and they are allowable.

Toyoizumi *et al.* describes an investigation into the effect of HSV-1 ICP34.5 combined with chemotherapeutic agents against human non-small cell lung cancer (NSCLC). Toyoizumi *et al.* concludes that the combination of HSV-based oncolytic therapy with chemotherapy may

improve efficacy over either individual modality alone in the treatment of NSCLC (see page 3013, Overview Summary). However, the chemotherapeutic agents were administered separately to the herpes simplex virus, *i.e.* they were not encoded by the genome of the herpes simplex virus.

Toyoizumi *et al.* briefly refers to studies by other researchers in which HSV amplicons carried IL-12 or IL-2 (page 3014, second column, second paragraph). However, this information does not teach the skilled person whether herpes simplex virus can successfully be used to deliver antisense molecules to down regulate a gene. For example, this does not teach the skilled person whether herpes simplex virus would express antisense molecules in the right part of the cell, or whether herpes simplex virus would be capable of expressing enough antisense molecules to have any effect. Nor does it teach the skilled person that HSV infection itself would not have an inhibitory effect on cellular antisense mechanisms. Furthermore, Toyoizumi *et al.* does not teach antisense molecules to SCCRO.

The Office contends that one of ordinary skill in the art would provide an antisense to SCCRO for anti-tumor therapeutics because Estilo *et al.* teaches that SCCRO mRNA correlates with metastasis of squamous cell carcinoma. Estilo *et al.* describes an investigation into the role of SCCRO and PIK3CA in the pathogenesis of oral tongue squamous cell carcinoma.

Development of novel antitumor strategies are mentioned on page 2305, column 1, third paragraph, where it is stated that "SCCRO may be a prognostic factor and provide a basis for the development of novel anti-tumor strategies". However, Estilo *et al.* does not state what these novel tumor strategies are or what they might be. In particular, it is not clear whether the basis for the development of novel tumor strategies is the finding that SCCRO may be a prognostic factor *per se*, or some other undisclosed strategy. In other words, the skilled person may interpret this statement as meaning that the ability to provide a prognosis based on the observation of SCCRO expression opens the way to new anti-tumor strategies that have nothing to do with SCCRO.

Moreover, Estilo *et al.* concludes that "additional studies are needed to prospectively correlate SCCRO expression with the development of nodal and assess its in reoperative planning" (page 2305, first column, second paragraph, emphasis added). Elsewhere, Estilo *et al.* notes that "the molecular mechanisms underlying the association between SCCRO and lymphatic metastasis remain to be elucidated" (see page 2303, column 2, second paragraph, emphasis added). Thus, rather than suggesting specific novel therapeutic strategies, Estilo *et al.* highlights uncertainties and suggests that additional studies should be undertaken. There is no teaching or suggestion in Estilo *et al.* that down-regulating SCCRO would provide an effective treatment for squamous cell carcinoma, and certainly teaching or suggesting of an antisense to SCCRO. In addition, Estilo *et al.* does not teach or suggest that herpes simplex virus may be used to deliver antisense nucleic acids.

The deficiencies in Toyoizumi and Estilo *et al.* are not made up by Jacobs *et al.* As discussed above Jacobs *et al.* is concerned with gene therapy, particularly with a non-invasive method of assessing the distribution of therapeutic gene expression. Jacobs *et al.* does not teach or suggest that herpes simplex virus may be used to deliver antisense nucleic acids. Furthermore, Jacobs *et al.* does not teach or suggest antisense molecules to SCCRO.

A prima *facie case* of obviousness has not been established because none of the cited references teach antisense to SCCRO. Even if the cited references taught or suggested each and every limitation present in the claims, which as discussed above they do not, to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. In addition, there must be some reasonable expectation that the proposed modification or combination would be successful. As Toyoizumi, Estilo *et al.*, and Jacobs *et al.* do not teach antisense to SCCRO, there is no motivation to produce the invention as claimed. Similarly, there would be no expectation that such an invention would be successful.

In view of the forgoing arguments, Applicants submit that no *prima facie* case of obviousness has been presented with respect to claims 1-3, 5-17, 19-28, 33-36, 42, 44, 45, 90, and 91 and respectfully request that this rejection be withdrawn.

Conclusion

In view of the amendments and arguments presented herein, a *prima facie* case of obviousness has not been established with respect to the pending claims. Applicants believe that the claims are in condition for allowance, and a notice to this effect is requested. If any matters remain before a Notice of Allowance is issued, the examiner is requested to telephone the undersigned at the telephone number below to discuss the case.

Respectfully submitted,

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